REMARKS

In response to the Examiner's Answer mailed April 13, 2010, and having a period for response set to expire on June 13, 2010, Applicant respectfully requests that the Examiner favorably consider the following remarks.

Amendments to the claims

With the present submission, claim 18 has been amended and new claims 40-49 have been introduced. Claims 1-17 and 21-32 were previously canceled. Thus, claims 18-20 and 33-49 are presently under consideration. Specifically, the preamble of claim 18 has been amended to recite a chemically modified double stranded short interfering nucleic acid molecule that mediates RNA interference. Claim 18, part (b) has been amended to recite the length of each strand as being between 18 and 24 nucleotides in length and having a range of 17 to 23 nucleotides being complementary to each other, *i.e.,* the number of base pairs in the duplex. Claim 18, part (c) has been amended to recite "the sense strand includes a terminal cap moiety at its 5'- and 3'-ends and the antisense strand includes a terminal cap moiety at its 3'-end". These amendments are supported by the instant specification as filed and detailed support is provided below.

The limitation of claims 18 and 40, part (b) *"each strand is between 18 and 24 nucleotides in length and 17 to 23 nucleotides of each strand are complementary to each other"* finds support at page 73, lines 1-5:

> *In one embodiment of the present invention, each sequence of a siNA molecule of the invention is independently 18 to 24 nucleotides in length, in specific embodiments about 18, 19, 20, 21, 22, 23, or 24 nucleotides in length. In another embodiment, the siNA duplexes of the invention independently comprise about 17 to about 23 base pairs (e.g., about 17, 18, 19, 20, 21, 22 or 23).*

The ranges of the number of nucleotides in the sequence of each strand and the number of nucleotides that are complementary to each other, i.e. the number of base pairs in the duplex, are drawn from the paragraph reproduced above from page 73 of the instant application that refers to "any siNA molecule of the invention" and thus can be used in combination with the chemical

modification features claimed in parts (c) and (d) of claims 18 and 40, which are drawn from the following paragraph of the instant application found on page 26, line 26 to page 27, line 11:

> *In one embodiment, the invention features a siNA molecule, wherein the sense strand comprises one or more, for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more phosphorothioate internucleotide linkages, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or about one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the sense strand; and wherein the antisense strand comprises about 1 to about 10 or more, specifically about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more phosphorothioate internucleotide linkages, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the antisense strand. In another embodiment, one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more, pyrimidine nucleotides of the sense and/or antisense siNA strand are chemically-modified with 2'-deoxy, 2'-O-methyl and/or 2'-deoxy-2'-fluoro nucleotides, with or without one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more, phosphorothioate internucleotide linkages and/or a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends, being present in the same or different strand.*

The claims, as amended, are therefore fully supported by the application as-filed, as well as by the priority applications, as explained in full details below. As such, no new matter is added. Applicants accordingly respectfully request entry of these amendments.

Priority

The Office declined to award the instant claims a priority that is earlier than January 14, 2004. Examiner's Answer, at pages 4-5. Applicant respectfully traverses the Office's priority determination and respectfully submits that the disclosure of the priority applications relied upon not only "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter", but also contains "a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains or with which it is most nearly connected,

to make and use the same". *Ralston Purina Co. v. Far-Mar-Co, Inc.,* 772 F.2d 1570, 1575 (Fed. Cir. 1985) and 35 U.S.C. § 112, ¶ 1 respectively.

The Office asserts that "[t]he applications do not teach the instant combination of limitations: each strand is 18-27 nucleotides in length, wherein 18-23 are complementary to each other and at least 18 nucleotides of the antisense strand are complementary to a target; in combination with 10 or more pyrimidine nucleotides of the sense and antisense strand being chemically modified with 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro; and in combination with the elements of the dependent claims." Office Action, at page 4. The Applicant respectfully traverses. Nevertheless, without acquiescing to the Office's position and in the interest of advancing prosecution and putting the claims in better condition for allowance or appeal, Applicant has amended claim 18 as described above. Furthermore, as described in greater detail below, the amendments and instant claims are supported by all of the following priority applications: parent application USSN 10/444,853, filed May 23, 2003; PCT/US03/05346, filed February 20, 2003; provisional application 60/408,378, filed September 5, 2002; provisional application 60/386,782, filed June 6, 2002; and provisional application 60/358,580, filed February 20, 2002.

USSN 10/444,853, filed on May 23, 2003, supports the instant claims as follows:

The limitation of claim 18 and 40, part (b) *"each strand is between 18 and 24 nucleotides in length and 17 to 23 nucleotides of each strand are complementary to each other"* finds support at page 73, lines 14-18:

> *In one embodiment of the present invention, each sequence of a siNA molecule of the invention is independently 18 to 24 nucleotides in length, in specific embodiments about 18, 19, 20, 21, 22, 23, or 24 nucleotides in length. In another embodiment, the siNA duplexes of the invention independently comprise about 17 to about 23 base pairs (e.g., about 17, 18, 19, 20, 21, 22 or 23).*

The limitations of claim 18 and 40, part (c) *"the sense strand includes a terminal cap moiety at its 5'- and 3'-ends and the antisense strand includes a terminal cap moiety at its 3'-end",* claim 18 part (d) *"10 or more pyrimidine nucleotides of the sense strand and antisense strand are chemically modified with 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro nucleotides",*

and claim 40 part (d) *"10 or more pyrimidine nucleotides of the sense strand or antisense strand are chemically modified with 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro nucleotides"*, all find support in the paragraph bridging pages 26 and 27:

> *In one embodiment, the invention features a siNA molecule, wherein the sense strand comprises one or more, for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more phosphorothioate internucleotide linkages, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or about one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the sense strand; and wherein the antisense strand comprises about 1 to about 10 or more, specifically about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more phosphorothioate internucleotide linkages, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the antisense strand. In another embodiment, one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more, pyrimidine nucleotides of the sense and/or antisense siNA strand are chemically-modified with 2'-deoxy, 2'-O-methyl and/or 2'-deoxy-2'-fluoro nucleotides, with or without one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more, phosphorothioate internucleotide linkages and/or a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends, being present in the same or different strand.*

The present claims are also fully supported by the motifs of Table IV and in numerous exemplary sequences shown in Table I and the Figures of the parent '853 application.

PCT/US03/05346, filed on February 20, 2003, supports the instant claims as follows:

The limitation of claim 18 and 40, part (b) *"each strand is between 18 and 24 nucleotides in length and 17 to 23 nucleotides of each strand are complementary to each other"* finds support at page 56, lines 4-8:

> *In one embodiment of the present invention, each sequence of a siNA molecule of the invention is independently 18 to 24 nucleotides in length, in specific embodiments about 18, 19, 20, 21, 22, 23, or 24 nucleotides in length. In another embodiment, the siNA duplexes of the*

invention independently comprise about 17 to about 23 base pairs (e.g., about 17, 18, 19, 20, 21, 22 or 23).

The limitations of claim 18 and 40, part (c) *"the sense strand includes a terminal cap moiety at its 5'- and 3'-ends and the antisense strand includes a terminal cap moiety at its 3'-end"*, claim 18 part (d) *"10 or more pyrimidine nucleotides of the sense strand and antisense strand are chemically modified with 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro nucleotides"*, and claim 40 part (d) *"10 or more pyrimidine nucleotides of the sense strand or antisense strand are chemically modified with 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro nucleotides"*, all find support in the paragraph bridging pages 19 and 20:

> *In one embodiment, the invention features a siNA molecule, wherein the sense strand comprises one or more, for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more phosphorothioate internucleotide linkages, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or about one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the sense strand; and wherein the antisense strand comprises about 1 to about 10 or more, specifically about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more phosphorothioate internucleotide linkages, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the antisense strand. In another embodiment, one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more, pyrimidine nucleotides of the sense and/or antisense siNA strand are chemically-modified with 2'-deoxy, 2'-O-methyl and/or 2'-deoxy-2'-fluoro nucleotides, with or without one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more, phosphorothioate internucleotide linkages and/or a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends, being present in the same or different strand.*

The present claims are also fully supported by the motifs of Table IV and in numerous exemplary sequences shown in Table I and the Figures of the '346 PCT application.

Provisional application 60/408,378, filed September 5, 2002, supports the instant claims as follows:

The limitation of claim 18 and 40, part (b) *"each strand is between 18 and 24 nucleotides in length and 17 to 23 nucleotides of each strand are complementary to each other"* finds support at page 38, lines 19-23:

> *In one embodiment of the present invention, each sequence of a siNA molecule of the invention is independently 18 to 24 nucleotides in length, in specific embodiments about 18, 19, 20, 21, 22, 23, or 24 nucleotides in length. In another embodiment, the siNA duplexes of the invention independently comprise about 17 to about 23 base pairs (e.g., about 17, 18, 19, 20, 21, 22 or 23).*

The limitations of claim 18 and 40, part (c) *"the sense strand includes a terminal cap moiety at its 5'- and 3'-ends and the antisense strand includes a terminal cap moiety at its 3'-end"*, claim 18 part (d) *"10 or more pyrimidine nucleotides of the sense strand and antisense strand are chemically modified with 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro nucleotides"*, and claim 40 part (d) *"10 or more pyrimidine nucleotides of the sense strand or antisense strand are chemically modified with 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro nucleotides"*, all find support at page 13, lines 5-20:

> *In one embodiment, the invention features a siNA molecule, wherein the sense strand comprises one or more, for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more phosphorothioate internucleotide linkages, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or about one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the sense strand; and wherein the antisense strand comprises about 1 to about 10 or more, specifically about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more phosphorothioate internucleotide linkages, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the antisense strand. In another embodiment, one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more, pyrimidine nucleotides of the sense and/or antisense siNA strand are chemically-modified with 2'-deoxy, 2'-O-methyl and/or 2'-deoxy-2'-fluoro nucleotides, with or without one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more, phosphorothioate internucleotide linkages and/or a terminal cap molecule at the 3'-end, the*

5'-end, or both of the 3'- and 5'-ends, being present in the same or different strand.

Numerous examples of modified siNA duplexes that meet the claim limitations can be also found in Table I and the Figures of the '378 provisional application. Support for the instant claims is therefore found not only in the above captioned paragraphs of the '378 application, but in numerous motifs and exemplary sequences shown therein.

Provisional application 60/386,782, filed June 6, 2002, supports the instant claims as follows:

The limitation of claim 18 and 40, part (b) *"each strand is between 18 and 24 nucleotides in length and 17 to 23 nucleotides of each strand are complementary to each other"* finds support at page 22, lines 16-19:

> *In one embodiment of the present invention, each sequence of a siNA molecule of the invention is independently 18 to 24 nucleotides in length, in specific embodiments about 18, 19, 20, 21, 22, 23, or 24 nucleotides in length. In another embodiment, the siNA duplexes of the invention independently comprise about 17 to about 23 base pairs (e.g., about 17, 18, 19, 20, 21, 22 or 23).*

The limitations of claim 18 and 40, part (c) *"the sense strand includes a terminal cap moiety at its 5'- and 3'-ends and the antisense strand includes a terminal cap moiety at its 3'-end"*, claim 18 part (d) *"10 or more pyrimidine nucleotides of the sense strand and antisense strand are chemically modified with 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro nucleotides"*, and claim 40 part (d) *"10 or more pyrimidine nucleotides of the sense strand or antisense strand are chemically modified with 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro nucleotides"*, all find support at page 10, lines 3-16:

> *In one embodiment, the invention features a siRNA molecule, wherein the sense strand comprises one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8 , 9 , or 10 phosphorothioate internucleotide linkages, and/or one or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more universal base modified nucleotides, and optionally a terminal cap molecule at the 3', 5', or both 3' and 5'-ends of the sense strand; and wherein the antisense strand comprises any of between 1 and 10, specifically about 1, 2, 3, 4, 5, 6, 7, 8 , 9 , or 10 phosphorothioate internucleotide linkages, and/or one or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more universal base modified nucleotides,*

and optionally a terminal cap molecule at the 3', 5', or both 3' and 5'-ends of the antisense strand. In another embodiment, one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 pyrimidine nucleotides of the sense and/or antisense siRNA stand are chemically modified with 2'-deoxy, 2'-O-methyl and/or 2'-deoxy-2'-fluoro nucleotides, with or without one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 phosphorothioate internucleotide linkages and/or a terminal cap molecule at the 3', 5', or both 3' and 5'-ends, being present in the same or different strand.

Numerous examples of modified siNA duplexes that meet the claim limitations can be also found in Table I and the Figures of the '782 provisional application. Support for the instant claims is therefore found not only in the above captioned paragraphs of the '782 application, but in numerous motifs and exemplary sequences shown therein.

Provisional application 60/358,580, filed February 20, 2002, supports the instant claims as follows:

The limitation of claim 18 and 40, part (b) *"each strand is between 18 and 24 nucleotides in length and 17 to 23 nucleotides of each strand are complementary to each other"* finds support at page 22, lines 12-15:

In one embodiment of the present invention, each sequence of a siNA molecule of the invention is independently 18 to 24 nucleotides in length, in specific embodiments about 18, 19, 20, 21, 22, 23, or 24 nucleotides in length. In another embodiment, the siNA duplexes of the invention independently comprise about 17 to about 23 base pairs (e.g., about 17, 18, 19, 20, 21, 22 or 23).

The limitations of claim 18 and 40, part (c) *"the sense strand includes a terminal cap moiety at its 5'- and 3'-ends and the antisense strand includes a terminal cap moiety at its 3'-end"*, claim 18 part (d) *"10 or more pyrimidine nucleotides of the sense strand and antisense strand are chemically modified with 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro nucleotides"*, and claim 40 part (d) *"10 or more pyrimidine nucleotides of the sense strand or antisense strand are chemically modified with 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro nucleotides"*, all find support in the paragraph spanning pages 9 and 10:

In one embodiment, the invention features a siRNA molecule, wherein the sense strand comprises one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8 , 9 , or 10 phosphorothioate internucleotide linkages,

and/or one or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more universal base modified nucleotides, and optionally a terminal cap molecule at the 3', 5', or both 3' and 5'-ends of the sense strand; and wherein the antisense strand comprises any of between 1 and 10, specifically about 1, 2, 3, 4, 5, 6, 7, 8 , 9 , or 10 phosphorothioate internucleotide linkages, and/or one or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more universal base modified nucleotides, and optionally a terminal cap molecule at the 3', 5', or both 3' and 5'-ends of the antisense strand. In another embodiment, one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 pyrimidine nucleotides of the sense and/or antisense siRNA stand are chemically modified with 2'-deoxy, 2'-O-methyl and/or 2'-deoxy-2'-fluoro nucleotides, with or without one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 phosphorothioate internucleotide linkages and/or a terminal cap molecule at the 3', 5', or both 3' and 5'-ends, being present in the same or different strand.

Numerous examples of modified siNA duplexes that meet the claim limitations can be also found in Table I and the Figures of the '580 provisional application. Support for the instant claims is therefore found not only in the above captioned paragraphs of the '580 application, but in numerous motifs and exemplary sequences shown therein.

Claim Rejections – 35 U.S.C. 112

The Office rejected claims 18-20 and 33-39 under 35 U.S.C. 112 first paragraph as allegedly introducing new matter. Applicant respectfully traverses the rejection. As described in the discussion of priority above, Applicant finds literal support for the instant claims in both the parent application and numerous priority applications as filed, and additionally has found numerous representative examples that are commensurate with the scope of the instant claims.

Claim Rejections – 35 U.S.C. 103(a)

The Office maintains its rejection of claims 18-20 and 33-39 under 35 U.S.C. § 103(a) as allegedly being obvious over Elbashir (The EMBO J. 2001, Vol. 20 (23), 6877-6888), in view of Matulic-Adamic (US 5,998,203), Parrish (Molecular Cell, 2000, Vol. 6, 1077-1087), and Crooke (U.S. 5,898,031). *See* Examiner's Answer at page 7. Applicants respectfully traverse.

Response to Arguments

With respect to the interpretation of the Elbashir reference, and in particular with respect to the teaching away aspects of this reference, the Examiner states that "the interpretation of the article has already been decided by the Board in the related appeal (Reexamination control 90/008,177, Patent 7,022,858), and the interpretation is consistent with that of the examiner in the instant rejection. The Examiner's rejection alleges that the teachings of Elbashir *et al.* and the other cited references would provide a "reasonable expectation of success given that each of the modifications were known in the art at the time of the invention was made to add benefits to antisense oligonucleotides, ribozymes, dsRNAs or siRNA duplexes". Examiner's Answer at page 13. The Examiner supports this position by stating that "the results of Elbashir *et al.* are considered to offer motivation to incorporate chemical modifications at various percentages to optimize the activity of the duplex because not all modifications result in activity at every percentage." Examiner's Answer at page 14. Applicant on the other hand, maintains that the teachings of Elbashir et al. provide a strong teaching away from the instant invention, or in the alternative at least provide such a high level of unpredictability so as to preclude one of skill in the art from having any reasonable expectation of success in arriving at or practicing the instant invention as of its effective filing date.

The interpretation of the Elbashir reference (which includes the same data and "siRNA user guide" teaching as the Tuschl II application) by the Board in a related appeal (Appeal 2009-002562, Reexamination control 90/008,177, Patent 7,022,858) is entirely consistent with Applicant's arguments. The Board correctly notes that "[a]ccording to both Tuschl I and Tuschl II, the absence of a 2'-OH group enhances the nuclease resistance of the 3'-overhang" and "Tuschl II preferably substitutes the 2'-OH groups of 3'-overhang (i.e., singled stranded) portion of siRNAs with OR groups to form C1-6 alkyl ester groups, e.g., methyl esters, and halide groups, e.g., fluoro, as well as replacing uridine residues with 2'-deoxy thymidines, to enhance the nuclease resistance of the overhang portion." Appeal 2009-002562, at pages 23-24. The Board also correctly states, "the most effective siRNA molecules are disclosed as having 3' overhangs (see e.g., FF 13, 18) and, therefore, would reasonably be expected to be more susceptible to nuclease degradation by virtue of being single stranded structures." Appeal 2009-

002562, at page 25. "Therefore, it would have been obvious to modify the 2'-OH group of the 3'-overhang of siRNAs to increase the nuclease resistance of the siRNA. The combination of chemical modifications known to increase the nuclease resistance of nucleic acid molecules to siRNA molecules, particularly to the 2'-OH group of a single stranded 3'-overhang, is likely to be obvious when it does no more than yield a predictable result." Appeal 2009-002562, at page 26. The Board concluded that because the *de minimis* requirements of claim 1 of the '828 patent could result in a siRNA in which the only modifications were in a 3'-overhang, that the '828 claims were obvious "because modifying just two 2'-OH groups at the 3' overhangs (ends) of the siRNA is within the scope of the claimed invention." *Id.*

Applicant respectfully notes that the instant claims differ significantly from the claims of US 7,022,828, which were at issue in Appeal 2009-002562. The '828 claims were directed to siRNA molecules having at least one 2'-O-methyl and at least one 2'-deoxy-2'-fluoro modification. The instant claims on the other hand, require terminal caps at the 5' and 3'-ends of the sense strand and the 3'-end of the antisense strand, in addition to 10 or more pyrimidine nucleotides of the sense strand and antisense strand being chemically modified with 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro nucleotides (claim 18) or 10 or more pyrimidine nucleotides of the sense strand or antisense strand are chemically modified with 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro nucleotides (claim 40). As such, as opposed to the claims of the '828 patent, the instant claims require more extensive modification well beyond that which was embraced by the prior art.

Applying the Board's reasoning in Appeal 2009-002562 to the instant claims would arrive at a different result because "[a] fair reading of [Elbashir]…is that more extensive 2'-deoxy or 2'-O-methyl modifications beyond the two nucleotide 3'-overhang reduces the ability of siRNAs to mediate RNAi". Appeal 2009-002562, at page 27. Clearly, the modifications as claimed are "more extensive" because they extend well beyond any 3'-overhang regions of the claimed short interfering nucleic acid molecules, and as opposed to modification of the 3'-overhangs only. The current claims require modification of (1) the 5' and 3'-ends of the sense strand in addition to (2) modification of the 5'-end of the antisense strand in addition to (3) modification of 10 or more pyrimidine nucleotides of both strands together (Claim 18) or (4)

modification of 10 or more pyrimidine nucleotides of at least one strand (Claim 40). The combination of these modifications, specifically features (1), (2), and (3) per claim 18 or features (1), (2), and (4) per claim 40 ***would not yield a predictable result and accordingly, one of skill in the art at the time of the invention would not have any reasonable expectation of success***. (emphasis added) Therefore, Applicant maintains that the Examiner's assertion that "it is a matter of routine optimization to determine an acceptable balance between a reduction in activity and an increase in stability, as long as the molecule is still in fact active" (see Examiner's Answer, pages 16-17) is clearly based on hindsight in view of Applicant's own teachings and ignores the teachings of the prior art that were available at the time of the instant invention.

Applicant respectfully maintains that the Office is attempting to argue that the instant invention is obvious because it was obvious to try and is the result of routine optimization. Applicant respectfully reiterates that the Federal Circuit has clarified the standard for a finding of obviousness based on an "obvious to try" standard in *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009). While acknowledging that, as stated by the U.S. Supreme Court in *KSR International Co. v Teleflex Inc.*, a skilled artisan, when motivated by an unmet need, can look to combine elements within the scope of the prior art, it would be improper to hold a claim obvious when:

> *what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result; where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful*

or

> *what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.*

To hold a claim obvious under these situations would be, according to the Federal Circuit, "succumb[ing] to hindsight claims of obviousness" and erroneous. *Id.* Reaffirming its prior holdings in *In re O'Farrell,* 853 F.2d 894, 903 (Fed. Cir. 1988), the Federal Circuit explained that in order for an "obvious to try" situation to serve as the basis for obviousness,

some direction in the prior art that would provide a reasonable expectation of success is still required. *See, O'Farrell,* at 903-04. Here, not only do the references cited by the Office provide no guidance as to what individual modifications when used "more extensively" can result in siRNA molecules that are both active and stable, they in fact indicate that extensive incorporation of these modifications into an siRNA was detrimental, or at least highly unpredictable. The prior art references therefore provide no guidance or any level of predictability that would allow one of skill in the art to have any reasonable expectation of success using the number and combination of modifications as presently claimed. Therefore, even an "obvious to try" inquiry fails to result in a finding of obviousness as one of skill in the art would simply have ***no reasonable expectation of success*** in practicing the instantly claimed invention.

The Office continues to argue that "in the instant case applicant is not claiming any specific combination or modification schematic that produces an unexpected result, but is rather claiming a huge genus of possible molecules wherein molecules within the genus are certainly considered obvious in view of the teachings of the prior art." Examiner's Answer, at page 26. Applicants respectfully maintain that the invention, when properly understood, is directed to a specific and uniform modification schematic that can be applied to any double stranded nucleic acid sequence as described in the specification. For example, application of the features of claim 18 to any duplex sequence will result in a specific structure with well defined features that include: The length of each strand, the number of base pairs in the duplex, caps at the 3' and 5'-ends of the sense strand and at the 3'-end of the antisense strand, and 10 or more pyrimidine nucleotides of the sense and antisense strand modified with 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro nucleotides. Application of the features of claim 40 to any duplex sequence will result in a specific structure with well defined features that include: The length of each strand, the number of base pairs in the duplex, caps at the 3' and 5'-ends of the sense strand and at the 3'-end of the antisense strand, and 10 or more pyrimidine nucleotides of the sense or antisense strand modified with 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro nucleotides. Application of these features provides surprising and unexpected properties to the genus of molecules as presently

claimed. Specifically, the instant invention provides short interfering nucleic acid molecules that possess both high serum stability coupled with a high level of RNAi activity.

Application of the features of claim 18 or 40 to a double stranded nucleic acid sequence of interest provides surprising and unexpected results that preclude any finding of obviousness in view of the failure of others. These unexpected results are clearly taught by the application as filed. For example, inspection of **Figure 3** of the instant application shows a direct comparison of the state of the art at the time of the invention (modified Elbashir duplex, Figure 4 on page 6882 of Elbashir *et al.*) to duplexes of the instant invention in terms of nuclease stability. The Elbashir duplex, having 3'-terminal 2'-deoxy modifications (See **Figure 3** of the instant application, SEQ ID NOs: 394 and 395), when tested in human serum, has a half life (T ½) of *15 seconds*. The duplexes of the instant invention however, all having 3' and 5'-caps of the sense strand and 3'-caps of the antisense strand combined with 10 or more 2'-deoxy-2'-fluoro pyrimidine modifications, all show dramatically improved nuclease stability: T ½ of *138 minutes* for SEQ ID NOs: 396 and 397; T ½ of *3.7 days* for SEQ ID NOs: 396 and 398; T ½ of *72 minutes* for SEQ ID NOs: 396 and 399; T ½ of *40 days* for SEQ ID NOs: 396 and 400; and T ½ of *32 days* for SEQ ID NOs: 396 and 401.

Additionally, the RNAi activity of duplexes of the invention, all having 3' and 5'-caps of the sense strand and 3'-caps of the antisense strand combined with 10 or more pyrimidine modifications (2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro), is surprisingly *comparable to or even improved* when compared to a control duplex of the prior art. See for example **Figure 14**, in which the siGL2 control (Elbashir duplex) is compared to duplexes of the invention having a "Stab 6" sense strand (sequence 30222, SEQ ID NO: 373) consisting of 3' and 5'-terminal caps with 2'-O-methyl and 2'-deoxy pyrimidine modifications and various "Stab 5" antisense strands, all having 3'-terminal caps with 2'-deoxy-2'-fluoro and 2'-deoxy pyrimidine modifications (sequence 30546, SEQ ID NO: 386; sequence 30224, SEQ ID NO: 374; sequence 30551, SEQ ID NO: 387; sequence 30557, SEQ ID NO: 388, and sequence 30558, SEQ ID NO: 389). Also, see for example **Figure 15**, in which the siGL2 control (Elbashir duplex) is compared to duplexes of the invention having a "Stab 4", "Stab 8" or "Stab 7" sense strand (sequence 30063,

SEQ ID NO: 372; sequence 30434, SEQ ID NO: 384; and sequence 30435, SEQ ID NO: 385 respectively) all consisting of 3' and 5'-terminal caps with 2'-deoxy, 2'-deoxy-2'-fluoro or 2'-O-methyl pyrimidine modifications and a "Stab 8" antisense strand having 3'-terminal caps with 2'-deoxy-2'-fluoro pyrimidine and phosphorothioate modifications (sequence 30430, SEQ ID NO: 375). As shown in these figures, the activity of the serum stable double stranded nucleic acid molecules of the invention is an *unexpected finding* in view of the teachings of the closest prior art.

The unexpected results, contrary to the teaching of the prior art are also clearly exemplified in **Figures 28, 29, and 30**, in which the RNAi activity of various duplexes of the invention (Stab 4/5; Stab 7/8, and Stab 7/11 respectively, all having sense strands with 3' and 5'-terminal caps combined with 2'-deoxy and 2'-deoxy-2'-fluoro pyrimidine modifications with ribo (Stab 4) or 2'-deoxy (Stab 7) purines and antisense strands having 3'-terminal caps with 2'-deoxy and 2'-deoxy-2'-fluoro pyrimidine modifications and with ribo (Stab 5), 2'-O-methyl (Stab 8) or 2'-deoxy (Stab 11) purines) are compared to an all RNA duplex control in inhibiting HBV gene expression in a dose response time course study. As shown in **Figures 28, 29, and 30**, the extensively and differentially modified duplexes of the invention all show comparable activity to the all RNA control at day 3, and *improved* activity at day 6 and day 9 time points.

As is clearly shown in **Figures 3, 14, 15, 28, 29, and 30** (amongst others), the double stranded nucleic acid molecules of the invention are significantly more stable than the double stranded nucleic acid molecules of the prior art, and surprisingly have retained or improved RNAi activity over the prior art molecules that allow these molecules to function as therapeutic modalities. The chemically modified duplexes of the instant invention are a significant and inventive advancement over the teachings of the closest prior art (Elbashir *et al.*) who teach that "more extensive" modification is detrimental to RNAi activity and whose attempts to more extensively modify such molecules resulted in *abolished* activity. Thus, even if the Office were able to make a *prima facie* showing of obviousness (which is not the case), the failure of others combined with the surprising and unexpected results as taught by the application as filed and priority documents, unequivocally preclude any finding of obviousness.

Conclusion

The instant claims are patentable. Applicants therefore respectfully request withdrawal of the standing rejections and allowance of the claims.

Respectfully submitted,

Date: April 22, 2010

/Peter Haeberli/
Peter Haeberli
Registration No. 52,980

Merck
1700 Owens Street, 4th Floor
San Francisco, CA 94158
Phone: (415) 814-8491
Email: peter_haeberli@merck.com